THE THERAPEUTIC USE OF RADIOACTIVE ISOTOPES

Lecture delivered at the Royal College of Surgeons of England

on

9th May 1958

by

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INTRODUCTION

RADIOACTIVE ISOTOPES FIRST became available for use in medicine in this country at the end of 1948. Their experimental use in the field of investigation has developed rapidly, though medicine has perhaps been slow to adopt these methods for the routine study of function in the living person in any but a few special hospitals and with the exception of the study of thyroid disorders.

The therapeutic use of radioactive isotopes was started in this country at the Royal Marsden Hospital in 1948. The main lines of what is being done to-day were established within the first year (Smithers, 1951), and until quite recently there seemed to be a distinct slowing down in initiative after the first rush of interest and enthusiasm. Existing radiotherapeutic methods were improved by the introduction of artificial radioisotopes, but only in the field of differential absorption was a quite new therapeutic development made possible.

TABLE I

RADIOACTIVE ISOTOPES MENTIONED IN THE TEXT

Isotope	Half-life	Maximum β-Energy (MeV)	Mean γ-Energy (MeV)
I^{131}	8 days	0·8	0·4
Na^{24}	15 hours	1·4	2·07
Br^{82}	36 hours	0·47	0·8
P^{32}	14·3 days	1·7	None
Au^{198}	2·7 days	0·96	0·41
Ag^{111}	7·6 days	1·0	0·3
Y^{90}	2·7 days	2·2	None
Cs^{137}	30 years	0·52	0·66
Co^{60}	5·3 years	0·31	1·25
Ta^{182}	111 days	0·5	1·1
Ir^{192}	75 days	0·67	0·60
Sr^{90}	28 years	0·61	None
Ce^{144}	280 days	0·30	0·1

The present therapeutic uses of artificial radioactive isotopes may be divided into six groups:

1. Differential absorption, using either inorganic or organic materials.
2. Surface application using either solid or fluid sources.

3. Instillation into the body for either direct local effect or for effect when transported elsewhere.
4. Infiltration, which is the equivalent of interstitial implantation using fluid sources.
5. Implantation, which may be either temporary or permanent.
6. Teletherapy using large sources, either at a short or long source-skin distance.

1. Differential absorption

The outstanding use of inorganic materials for therapeutic irradiation by differential absorption has been radioactive iodine (I^{131}). This material has been used primarily for the treatment of thyrotoxicosis and thyroid carcinoma. Except for some minor uptake in the salivary glands, iodine localizes well in the thyroid to the comparative exclusion of other tissues and can be used for depressing thyroid function by destruction of the gland itself. Its use in thyrotoxicosis and thyroid carcinoma has been the subject of another lecture in this series and will not be dealt with further here.

When the radioactive uptake by the thyroid has been blocked by previous administration of inactive iodine, I^{131} may then be given for general distribution through the circulation and has been used in a few cases for the treatment of disseminated radiosensitive carcinomas and for multiple myelomatosis but without any great success. I^{131} labelled human serum albumin has been used in the same way (Kriss, Bierman, Thomas and Newell, 1955; Kay, Ledlie and Sbresni, 1958), and so has radioactive sodium (Na^{24}).

The other inorganic substance widely used for differential absorption is radioactive phosphorus (P^{32}). The demand of growing cells for phosphorus leads to some slight differential uptake in tumours which are growing rapidly. This has been frequently demonstrated and can be used at times as a diagnostic test, for example in the brain (Selverstone, Solomon and Sweet, 1949), eye (Palin and Tudway, 1955; Terner, Leopold and Eisenberg, 1956), or cervix uteri (Papaloucas, 1958). The difference in uptake between the most rapidly growing tumours and some normal tissues, however, is seldom sufficient to make this method of much therapeutic value. The damage done to the bone marrow, for example, by P^{32} usually outweighs its value for generalized disseminated radiosensitive tumours, though a few dramatic results have been reported (Smithers, 1951).

The chief use of P^{32} in therapeutics has been in the treatment of polycythaemia vera (Erf and Lawrence, 1941; Harman, Hart and Ledlie, 1955), haemorrhagic thrombocythaemia (Fountain, 1958; Alphos, Field and Ledlie, 1958), lymphatic leukaemia (Osgood, 1951), lymphosarcoma, reticulum-cell sarcoma, and some early cases of Hodgkin's disease (Low-Beer, 1954).

Interest at present lies chiefly in finding methods of increasing the differential absorption of radioactive materials in selected tissues, mostly through the use of hormones. The best example is the use of thyroid stimulating hormone from the pituitary to persuade thyroid tumours to take up more iodine. Another interesting example is the use of testosterone in an attempt to promote localization of P^{32} in metastases in bone (Maxfield, Maxfield and Maxfield, 1958).

It is to be hoped that further development in this direction will take place, since the effect of radioactive isotopes on the control of disseminated tumours, when good localization can be obtained, may be dramatic and occurs at a time when other effective treatments for these patients are seldom available. Little work has yet been done, for instance, on the tumour localization of labelled organic materials and more is needed on the localization of inert particles by the reticuloendothelial system, using radioactive colloids (Hahn, Carothers, Hilliard, Bernard and Jackson, 1956).

2. Surface application

The surface application of radioactive isotopes may be carried out with either fluid or solid sources, used either for their beta- or gamma-ray emissions.

Solid radioactive isotopes employed as gamma-ray sources for surface applications are usually radioactive cobalt (Co^{60}), radioactive tantalum (Ta^{182}), and radioactive iridium (Ir^{192}). Co^{60} has been used in a number of forms, usually as rods or needles applied on a mould, but has also been incorporated as a powder in a malleable material which is moulded directly on to the surface (Becker and Scheer, 1951). Ta^{182} has been used mostly as wire which is wound on to a prepared mould (Fig. 1). Ir^{192}, with its softer gamma-ray emission, has not been much in the field for surface application but, as a large source held at a short distance from the skin, it gives an energy absorption distribution in the tissues very similar to a radium applicator and is useful as an alternative to such radium techniques (Mitchell and Haybittle, 1958).

Solid sources used for beta-ray applicators have mostly contained radioactive strontium (Sr^{90})—usually in the form of foil—and have been chiefly employed in ophthalmology (Lederman and Sinclair, 1956). P^{32} has been incorporated in a plastic sheet from which many applicators of varied shape may be cut and applied for the treatment of the most superficial lesions (Sinclair and Blondal, 1952). A rather elegant beta-ray applicator has also been made using radioactive cerium (Ce^{144}) (Haybittle, 1953).

Fluids for surface application have been used predominantly in the bladder. The fluid may be inserted in a bag which distends the bladder, irradiating the whole of the mucosal surface from within (Fig. 2) (Wallace, Walton and Sinclair, 1949). Isotopes made use of in this way have been Na^{24}, radioactive bromine (Br^{82}), and Co^{60} (Müller, 1949). Fluid suspensions of inert radioactivated particles have also been employed for surface application without the necessity of using a bag, by instilling the non-absorbable fluid directly into the cavity concerned. Again the bladder has been the site where this method has been most often applied and both radioactive gold (Au^{198}) and radioactive yttrium (Y^{90}) colloids

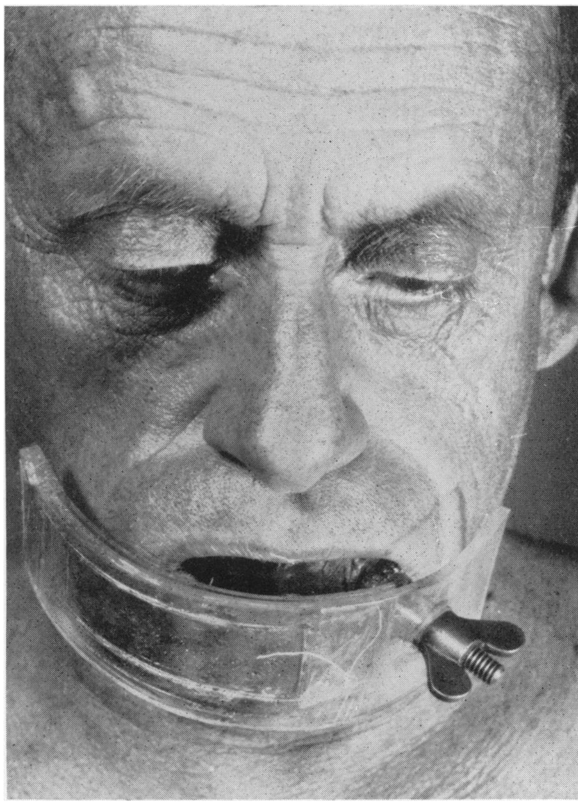

Fig. 1. Radioactive tantalum wire applied on a mould.

have been employed (Ellis and Oliver, 1955; Mackay, Smithers and Wallace, 1958). These methods are sometimes applicable to other body cavities and to artificially created cavities following the removal of tumours where it is thought advisable to irradiate the tumour bed owing to the risk of neoplastic cells remaining.

Pleural and peritoneal effusions due to neoplastic infiltration have been treated with Au^{198} colloid (Müller, 1950; Walton and Sinclair, 1952; Mackay, 1957). With rapidly recurring effusions necessitating repeated aspirations, this treatment may at times be most effective as a palliative measure.

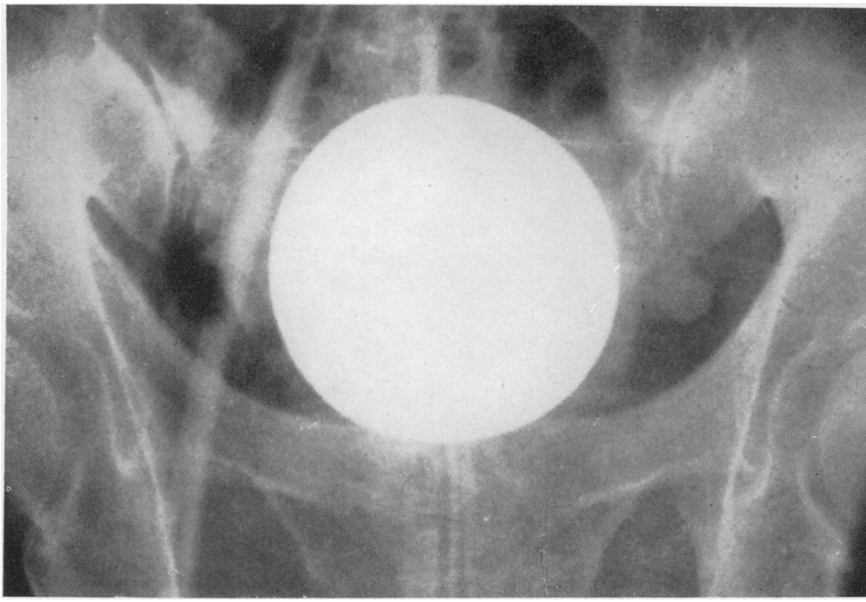

Fig. 2. Bag in the bladder for the application of radioactive fluids.

3. Instillation

Instillation into the body for absorption rather than surface application has been attempted experimentally, chiefly in the hope of concentration of the material in the regional lymph nodes. Colloidal Au^{198} and radioactive colloidal silver (Ag^{111}) have been tried, and silver-coated Au^{198} particles and carbon particles plated with Au^{198} (Hahn, 1956). The favourite site for this work has been the lung and some interesting experimental work has been done in dogs (Bryant, Berg and Christophersen 1953 ; Wheeler, Jaques, Allen, Soltes, O'Conor and Black, 1956). An extension of this work has been the direct injection of radioactive material into the pulmonary artery by cardiac catheterization (Müller and Rossier, 1951 ; Pochin, Cook, Cunningham, Hollman, Hudswell and Payne, 1954). While there is no doubt that good localization can sometimes be obtained in this way and that interesting differences have been found between the rates and degrees of absorption in lymph nodes of materials with different particle sizes and of different chemical composition, the method so far has been of little practical value.

4. Infiltration

Direct tumour infiltration with radioactive materials is the equivalent of an implant using a fluid medium. A number of materials have been used for this purpose, P^{32}, colloidal Au^{198}, chromic radiophosphate and others. Such infiltration has been done in the prostate (Flocks, Kerr, Elkins and Culp, 1952 ; Bulkeley, Cooper and O'Conor, 1956), in the parametrium (Kottmeier, 1954), and in various tumours, particularly those forming fixed masses in the neck which are inoperable and have persisted after previous external irradiation.

The raising of tissue tension by the injection under pressure of fluids into tumours would seem likely to increase the risk of spread, and this method has not been regarded with much favour despite some isolated reports of a dramatic response. It can be a useful method of palliative treatment in a few instances where dissemination has already taken place and the local tumour presents a difficult problem for external irradiation or implant.

5. Implantation

Radioactive isotopes of short half-life may be employed for permanent implants and of longer half-life for temporary implants in much the same way as radium has been used for so long. The chief materials employed

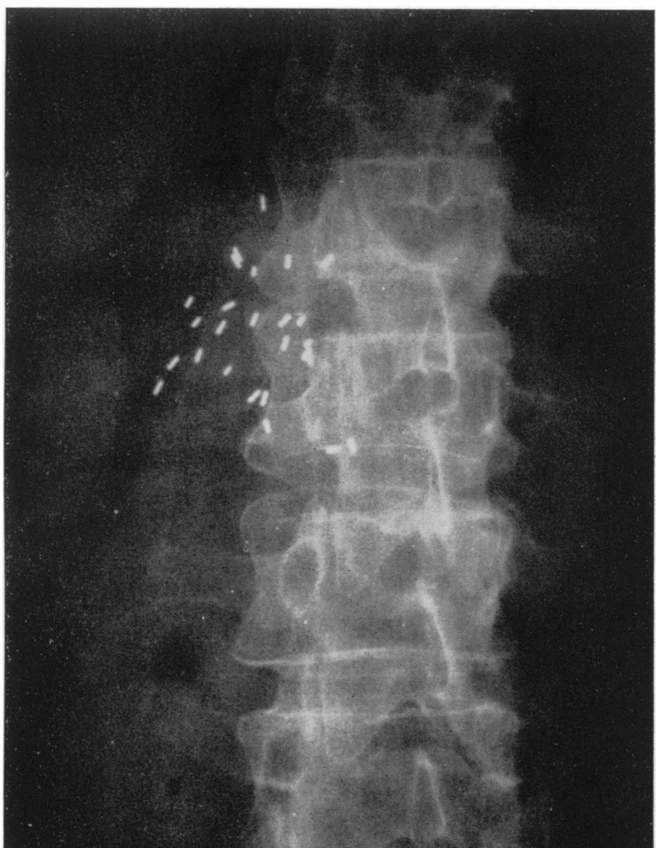

Fig. 3. Radioactive gold grains implanted into a carcinoma of the pancreas.

as radium substitutes in implant work have been Co^{60} (Meschan, Edwards and Rosenbaum, 1951) either in tubes or needles or as small grains contained in plastic tubing (Morton, Callendine and Myers, 1951), and Ta^{182} in the form of wire (Wallace, Stapleton and Turner, 1952), removable when treatment is completed. The most successful of these methods so far has been the Ta^{182} wire implantation of bladder tumours (Mackay, Smithers and Wallace, 1958). Ir^{192} has also been used in small grains contained in nylon tubing for temporary implants, but this material is also useful for permanent implants and has been employed with advantage in this way by Henschke (1957). Multiple small sources of this kind have been extensively used as a substitute for radon seeds, and Au^{198} grains

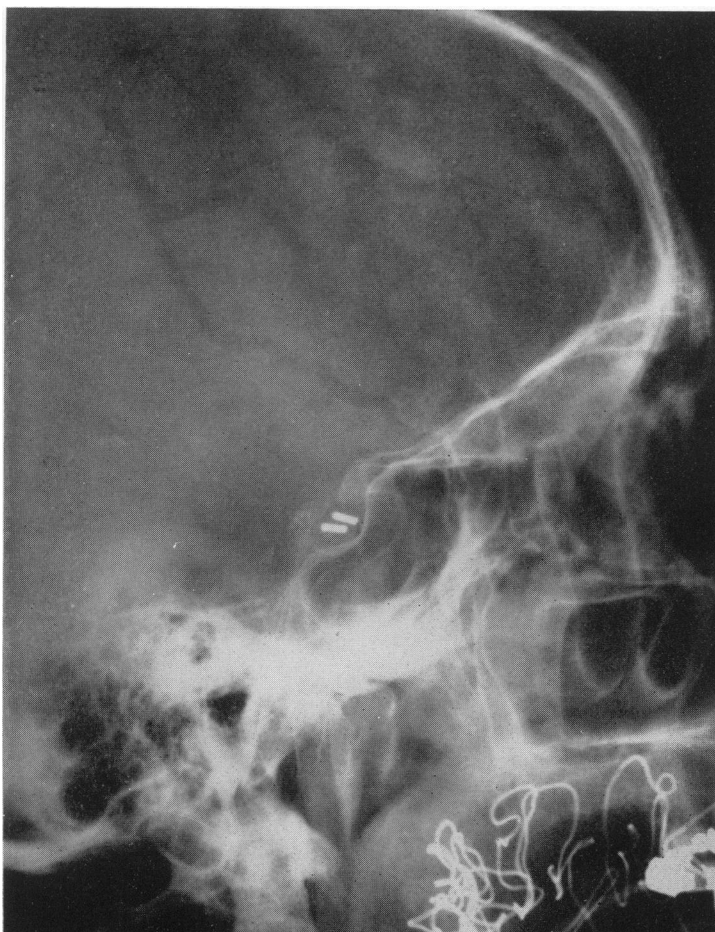

Fig. 4. Radioactive yttrium rods implanted in the pituitary.

particularly have been implanted (Hodt, Sinclair and Smithers, 1952) into a wide variety of tumours throughout the body (Fig. 3). These are permanent implants made with an isotope of short half-life. Pure beta-ray emitters may be useful for permanent implants and Y^{90} has been used for pituitary destruction (Fig. 4) in the treatment of some hormone-dependent tumours mostly of the breast (Forrest, 1957; Greening, 1957).

Some artificial radioactive isotopes have a notable advantage in implant work: they may be kept always ready for use in the operating theatre. An implant can then be done at the time of exploration if a tumour is found to be irremovable, and a major operation not leading to an attempt at any effective treatment avoided. The two sites at which such implants have been most frequently done have been the stomach (Fleming and Barrett, 1955), and the lung (James, Henschke and Myers, 1953; Cleland, 1958).

These new methods of radioactive implantation differ in no essentials from the old, but they have added variety and given a new flexibility to these procedures.

6. Teletherapy

Large sources of radioactive materials are useful for beam therapy and have been employed as such for many years in the form of teleradium units, from the days of the 1 gramme "bomb" to the present-day 10-12 gramme teleradium units. Apart from Ir^{192} already mentioned, the other radioactive materials so far inserted into teletherapy units have been radioactive caesium (Cs^{137}) and Co^{60}.

Cs^{137} is a fission product obtained by separation from waste in atomic energy plants. It is used in treatment units as a substitute for 250kV X-radiation, providing a beam of better quality with less differential bone absorption while being comparatively cheap to install and trouble-free to run. It has a convenient half-life of thirty years. Smaller units for treatment of more superficial head and neck tumours are also being designed using Cs^{137}. These are a possible replacement for the teleradium units at present in use.

Teletherapy with radioactive isotopes has been chiefly developed with Co^{60} sources in 1,500-2,000 curie units as a substitute for supervoltage X-ray machines. These emit gamma-rays of 1·17 and 1·33 MeV but are approximately equivalent to 3 MeV X-rays in quality because of the softer components contained in X-ray beams which are designated by their peak voltage. The improved depth-dose and quality of Co^{60} teletherapy units are raising the standard of palliative X-ray therapy for deep-seated malignant disease. Their output of radiation and the sharpness of the edges of their beams are not, however, as satisfactory as those of the corresponding supervoltage X-ray plants in the 2-4 million volt range. While this may be of little consequence in large-field palliative treatment, it can be a real disadvantage in the accurate localization of high dose treatment with economy of total energy absorption in attempts at curative therapy. Another disadvantage is the comparatively short half-life of Co^{60}, requiring replacement of the source every few years and continuous attention to the changing dose-rate. Nevertheless, these are most valuable smooth-running units, requiring no staff of technicians for their maintenance and comparatively cheap to run. They seem destined to be the major source of beam therapy for the routine treatment of tumours some depth below the surface in all but the largest radiotherapy departments for some years to come.

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THE HAND CLUB of Great Britain and the Second Hand Club are holding an open meeting at the Royal College of Surgeons on Saturday, November 22, from 10 a.m. to 4 p.m. with lunch at the College.

Any surgeon interested in Hand Surgery is invited to attend. Further particulars may be obtained from the Hon. Secretary, The Second Hand Club, H. Graham Stack, 150, Harley Street, W.1.

MONTHLY DINNERS

MONTHLY DINNERS ARE held in the College on the Wednesday before the second Thursday of each month. The following are entitled to attend with their guests : all diplomates and students of the College and members of the Associations linked to the College through the Joint Secretariat. It is not necessarily intended that guests should be members of the medical profession.

The next four dinners will be held at 7 for 7.30 on 8th October, 12th November, 10th December and 7th January.

The cost is £1 10s. 0d., which includes cocktails before dinner and wine at the table. Applications for tickets, accompanied by a cheque for the appropriate amount, must be sent to the Deputy Secretary at least a week before the date of the dinner. Cheques should be made payable to " Royal College of Surgeons of England." The dress is lounge suit.